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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,607	01/30/2001	Ib Jonassen	4409-214-US	2082

7590 03/18/2004

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,607	JONASSEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-55 and 57-59* is/are rejected.

7)☒ Claim(s) *56* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 48-59 are pending.

Applicants' amendment filed January 12, 2004 is acknowledged. Applicants' response has been fully considered. Claims 1-47 have been cancelled, and new claims 48-59 have been added. Therefore, claims 48-59 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 20-32 and 34-46 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed January 12, 2004.

3. The previous rejection of claims 20-32 and 34-47 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claim, and applicants' response at pages 7-8 in the amendment filed January 12, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 48-55 and 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, or, a derivative of GLP-1 or a specific GLP-1 analog having the same amino acid sequence as SEQ ID NO:2 with a lipophilic substituent, wherein a lipophilic substituent having 8-40 carbon atoms and optionally having an

amino group is optionally via a spacer of Lys, Glu, Asp, Glu-Lys or Asp-Lys attached to the C-terminal amino acid, does not reasonably provide enablement for a derivative of GLP-1 analog, wherein the lipophilic substituent is optionally via a spacer of Lys, Glu, Asp, Glu-Lys or Asp-Lys attached to the C-terminal amino acid, where the sequence of GLP-1 analog is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 48-55 and 57-59 are directed to a derivative of GLP-1 or an analog thereof, wherein a lipophilic substituent is optionally via a spacer attached to the C-terminal amino acid of GLP-1. The specification, however, only discloses cursory conclusions (pages 2-5) without data supporting the findings, which state that the invention relates to the derivatives of peptide hormones such as GLP-1 or GLP-2 which have been modified by introducing a lipophilic substituent comprising 8-40 carbon atoms in the C-terminal amino acid of the native peptide or analog thereof. There are no indicia that the present application enables the full scope in view of the derivative of GLP-1 analog containing the lipophilic substituent as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the analogs of GLP-1 in the lipophilic-containing derivatives, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed variants for the derivatives except the derivative of a specific GLP-1 analog, SEQ ID NO:2 (page 6), and determination of the protraction of a somatostatin derivative in pigs (Example 4). There are no other derivatives of GLP-1 analogs being made or used.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Wagner *et al.*, WO 95/03405) indicates a recombinant polypeptide such as GLP-2 having modification at Nα-terminus or C-terminus produces a polypeptide is longer acting and more potent than the naturally occurring polypeptide; Muranishi *et al.* (J. Controlled Release 19, 179-188 (1992)) teach three modified peptide hormones such as thyrotropin-releasing hormone, tetragastrin and insulin having the fatty acid moieties (acyl chains) attached to their N-termini. However, these references do not teach the modified GLP-1 analog containing a lipophilic group, furthermore, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of GLP-1 analogs in the derivatives, and the pharmacological effects of the GLP-1 to be considered enabling for the claimed variant.

(4). Predictability or unpredictability of the art:

The specification has shown one GLP-1 derivative, SEQ ID NO:2. However, the specification has not demonstrated the make and use of derivatives of various GLP-1 analogs, nor has shown the effects of the derivatives, the invention is highly unpredictable regarding the effect of the derivative in the treatment of diseases.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to derivatives of GLP-1 or analogs thereof containing lipophilic substituents attached to the C-terminal amino acid of GLP-1 or GLP-1 analogs. The specification indicates the derivatives of peptide hormones such as GLP-1 or GLP-2 which have been modified by introducing lipophilic substituent comprising 8-40 carbon atoms in the C-terminal amino acid of the native peptide or analog thereof, where the analogs are the parent peptides having deletion, substitution or addition of one or more amino acids in the sequences (pages 2-5), and determination of the protraction of a somatostatin derivative containing a lipophilic group in pigs (Example 4). However, the specification has not demonstrated the making and use of any derivative of GLP-1 analogs except for SEQ ID NO:2. There is no working example demonstrating the effect of the derivative. Since the specification fails to provide sufficient teachings on the identities of various GLP-1 analogs in the derivatives and the effect of the derivative in treating various diseases, it is necessary to carry out further experimentation to make the derivatives and to assess the effect of the derivatives containing various GLP-1 analogs.

(6). Nature of the Invention

The scope of the claims encompasses many structural variants of GLP-1 analogs in the derivative, but the specification has not provided sufficient teachings regarding the identities of the GLP-1 analogs in the derivatives and the effects of the derivatives. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the effects of claimed compound is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the derivatives containing various GLP-1 analogs.

In response, applicants indicate the amended claims are directed to C-terminally modified GLP-1 or analogs thereof, where the modifcation is the attachment of an 8-40 carbon lipophilic group optionally via a spacer to the C-terminal amino acid of the peptide, and the specification teaches the claimed derivatives are produced via the formation of an amide bond, and the derivative of the invention have a protracted profile of action relative to the unmodified parent peptide (pages 3-4, pages 12-13); the Examiner's rejection is based on the presence of a single working example of the claimed GLP-1 derivatives, which does not mean the claims to such products are nonenabled; the Examiner fails to describe why the teachings on pages 2-5 of the specification would not enable one to successfully produce the claimed derivatives via amide bond formation; the reference of Knudsen et al. (J. Med. Chem. 2000) provides additional evidence that the claimed C-terminally modified GLP-1 derivatives could be readily produced and tested for protraction by following the teachings of the specification; and regarding "the sequences of GLP-1 analogs are not defined", the sequence of GLP-1 (7-37) was known before the 1995 filing date of the instant application, and the methods for preparing analogs of GLP-1

(7-37) are also known to those of ordinary skill in the art (pages 4-6 of the response). The response has been considered, however, the argument is found not fully persuasive because the claims encompass many variants of GLP-1 analogs for the derivatives, where the structural characterization and pharmacological effects of the analogs are not cited, and the specification does not provide sufficient teachings regarding the identities of these variants and their pharmacological effects, the analysis of In re Wands factors (see the section above) provides the evidence that the undue experimentation is required. For example, the specification only provides a specific derivative of GLP-1 analog, SEQ ID NO:2, and the protraction of a somatostatin derivative, however, the protraction of SEQ ID NO:2 or any derivative containing GLP-1 is not demonstrated. Regarding the production of the claimed C-terminally modified GLP-1 derivatives via amide formation and GLP-1 sequence, the argument is persuasive, thus the attachment of an 8-40 carbon lipophilic group optionally via a spacer to the C-terminal amino acid of GLP-1 is enabled. Although the methods for preparing analogs of GLP-1 were well known to the one of ordinary skill in the art, the identities of the active GLP-1 analogs are not provided, thus it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the derivatives containing various GLP-1 analogs.

5. Claim 56 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

6. Claims 48-55 and 57-59 are rejected, and claim 56 is objected to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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March 12, 2004

ROBERT A. WAX
PRIMARY EXAMINER